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*Annex to the request for a patent grant*

Information about additional inventors:  
Preparation of tetrazole derivatives in a novel crystal form

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## Preparation of tetrazole derivative in a novel crystal form

### Field of the invention

(IPC<sup>7</sup> C 07 D 403/10, A 61 K 9/19)

The present invention belongs to the field of chemistry of heterocyclic compounds and pharmaceutical industry and relates to a novel crystal form of a pharmaceutically useful crystalline potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole and the new mode of its preparation.

### Technical problem

2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole, known under the generic name losartan, acts on the last step of the cascade renin-angiotensin system by binding to the angiotensin II receptor. By utilizing said biochemical effect losartan is generally used as an effective antihypertensive agent in the form of a potassium salt (hereinafter referred to as losartan potassium). In pharmaceutical compositions it is often combined with diuretics.

There is a need for losartan and the salt thereof, respectively, of high purity in such a form to be simply incorporated into a pharmaceutical formulation which provides high bioavailability. For incorporation into a pharmaceutical formulation, pharmaceutical active substances must have defined desired physicochemical properties and in addition to high purity, suitable stability, nonhygroscopicity, appropriate solubility and compatibility with the excipients are demanded.

Prior art

The substituted imidazoles with an action on the renin-angioten system of the blood pressure regulation are disclosed in EP 253310 and US Pat. No. 5,138,069.

It is known that losartan potassium exists in several polymorphic forms [K. Raghavan et al., Pharm. Res., 1993, 10, 900-904; L. S. Wu et al., Pharm. Res., 1993, 10, 1793-1795]. The authors of US Pat. No. 5,608,075 present that polymorphic form I, characterized by DSC endotherm at 229.5°C, while heating transforms to polymorphic form II characterized with the endothermic peak of melting at 273.2°C. Form I is stable at room temperature, Form II is stable at higher temperatures. Therefore, Form II gradually converts to thermodynamically more stable Form I under normal conditions of handling.

SI 200300145 describes a potassium salt of substituted imidazole in a polymorphic form with the bound water (water content 7 to 12 weight percent) named Form III. The patent discloses that Form III was isolated in the form with three bound molecules of water *per* molecule of the active substance, and at heating the polymorphic form with two bound molecules of water *per* molecule of the active substance was also formed. Physical analysis of that form has shown that it is a polymorphic form in the form of dihydrate thus with two crystal-bound molecules of water *per* molecule of the active substance. The authors of the patent WO 03048135 succeeded in preparing a similar substance – a polymorphic form with the bound water between 12% and 16% (wt. %). Said patent also discloses further two polymorphic forms of potassium salt characterized by peak diffractions on the powder diffraction pattern at about 4.3, 15.6 and 23.4 degrees 2θ named Form IV, and another polymorphic form named Form V characterized by peak diffractions on the powder diffraction pattern at about 6.4, 12.2, 20.7, 21.5 and 22.5 degrees 2θ.

Likewise, SI 200300025 discloses the preparation of alkali or alkali-earth salts of losartan in the form of a fine amorphous powder by lyophilization of an aqueous

solution of alkali or alkali-earth salt of said substituted imidazole, or the same by evaporation according to SI 200200145.

It is known that a defined form of a polymorph itself does not provide demanded suitable physicochemical properties. In US Pat. No. 5,859,258 losartan of polymorphic form I was crystallized from a mixture of *i*-propanol and 2.4–2.6% of water. It has been found that uncontrolled crystallization may result in formation of large three-dimensional complexes which are inappropriate for incorporation into a pharmaceutical formulation, and the patent discloses the very rigorously controlled process demanding fulfilment of 14 different conditions in order to obtain the desired morphology of the particles for pharmaceutical use.

From the prior art it is evident that an essential element for the preparation of crystal forms of losartan potassium with the bound water is the presence of water in a combination with a suitable solvent or the presence of water in the form of atmospheric humidity. The crystal form with about 7 to about 12% water was isolated from a combination of solvents and water or by exposing of the amorphous substance to atmospheric humidity, and the crystal form with from 12 to 16% water was prepared only by exposure of amorphous losartan potassium or by relatively long exposure of losartan potassium of form I to controlled atmospheric humidity above 80% relative humidity.

Unlike US Pat. No. 5859258 where losartan potassium of form I was crystallized from a combination of alcohol and water and according to WO 03048135 preparation of a polymorphic form Form IV can be prepared by dissolving losartan potassium in a solvent with a melting point below 135°C and the addition of dichloromethane whereupon the suspension is formed, and a polymorphic form Form V by dissolving losartan potassium in a solvent with a melting point below 135°C and the addition of hexane. For both processes the patent lists alcohols having from 1 to 6 carbon atoms as the most preferred solvents, and in the examples only ethanol is set forth.

#### Description of the figures

Figure 1: X-ray powder diffractogram of a polymorphic form X of losartan potassium salt.

Figure 2: DSC diagram of a polymorphic form of losartan potassium prepared by the procedure described in Example 4.

### Description of the invention

The object of the present invention is a completely novel crystalline form of losartan potassium.

In view of the process disclosed in WO 03048135 which describes the formation of Form V from the solvent system comprising one of C<sub>1</sub> – C<sub>6</sub> alcohols and hexane, it would be expected that the polymorphic form with peak diffractions on the X-ray powder diffractogram at about 6.4, 12.2, 20.7, 21.5 and 22.5 degrees 2θ would be isolated from the solvent system methanol – hexane.

Surprisingly, it has been found that a completely new polymorphic form, with peak diffractions on the X-ray powder diffractogram at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29.2 degrees 2θ, is obtained if a potassium salt of losartan of form I is dissolved in methanol, the resulting solution is concentrated to a dense glassy mass, and while stirring poured into hexane, the resulting particulate is filtered and carefully dried,

It is interesting that the same crystalline form is obtained together with already known polymorphic form I if losartan potassium of form I is dissolved in a mixture of methanol and water and the resulting solution is concentrated and while stirring at room temperature is poured into diisopropylether.

We have named a crystalline form of a potassium salt of losartan characterized with peak diffractions on the X-ray powder diffractogram at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29.2 degrees 2θ polymorphic form X. Regarding the mode

of isolation, the present invention also relates to the solvates of polymorphic form X of losartan potassium.

The present invention further relates to the pharmaceutical compositions comprising polymorphic form X of losartan potassium or the solvates of polymorphic form X of losartan potassium. The appropriate daily dose contains 1 to 500 mg of polymorphic form X of losartan potassium and may also contain the other suitable active substances, for example, a diuretic.

The pharmaceutical composition may be in a dosage form suitable for oral or parenteral administration and is indicated, for example, for the treatment of hypertension, the pharmaceutical composition, the object of said invention, for example, can be in the form of tablets, capsules, pellets, granules and suppositories. Solid pharmaceutical dosage forms can be coated, for example, with the aim to improve pelletability, or to adjust disintegration and absorption, respectively.

According to the object of the present invention, the film coated tablets may be prepared by the direct dry blend procedure or by the wet granulation method or any other suitable procedure known in pharmaceutical technology.

#### Experimental part

##### X-ray powder diffraction (XRD)

An apparatus Philips PW1710 using the reflexion technique under the conditions:  $\text{CuK}\alpha$  radiation, range from  $2^\circ$  to  $37^\circ 2\theta$  with a  $0.04^\circ 2\theta$  step, integration time 1 second was used.

A typical diffractogram of polymorphic form X of losartan potassium is shown in Figure 1.

##### Differential thermal calorimetry (DSC)

A DSC thermogram of the sample isolated according to the procedure described in Example 4 is shown in Figure 2. With repeated recording of the dried sample an essentially identical DSC thermogram was obtained.

In the following examples which illustrate but in no way limit the present invention, the best modes for the preparation of novel pharmaceutically useful polymorphic form of losartan of the present invention are presented.

#### **Example 1**

##### **(Preparation of an amorphous potassium salt of losartan)**

29.3 g of purified losartan was suspended in 293 ml of water. At room temperature pH was adjusted to 9.3 with a 10% aqueous potassium hydroxide solution. The reaction mixture clarified. The solution was filtered and lyophilized. A white, completely amorphous product was obtained; yield 31.8 g.

#### **Example 2**

10 g of a potassium salt of losartan of form I was dissolved in a mixture of 200 ml of methanol and 1.2 ml of water. The resulting solution was concentrated to the volume of 13 ml and while stirring at room temperature it was poured into 500 ml of diethyl ether. The resulting precipitate was stirred at room temperature for 1 hour, filtered and dried *in vacuo* at 45°C. Yield 9.3 g.

#### **Example 3**

##### **(Preparation of a potassium salt of losartan containing polymorphic form X)**

10 g of a potassium salt of losartan of form I was dissolved in a mixture of 200 ml of methanol and 1.2 ml of water. The resulting solution was concentrated to the volume of 35 ml and while stirring at room temperature it was poured into 500 ml of diisopropylether. The resulting precipitate was stirred at room temperature for 1 hour, filtered and dried. Yield 9.93 g.

**Example 4****(Preparation of polymorphic form X of a potassium salt of losartan)**

1 g of a potassium salt of losartan of form I was dissolved in 20 ml of methanol. The resulting solution was concentrated to a dense glassy mass and while stirring at room temperature it was poured into 100 ml of *n*-hexane. The resulting precipitate was stirred at room temperature for 1 hour and filtered. It was carefully dried. Yield 0.92 g.

Claims

1. Polymorphic form X of a potassium salt of losartan characterized in that it exists in a crystalline form and its X-ray powder diffractogram has diffractions at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29.2 degrees 2 $\theta$ .
2. Polymorphic form X of a potassium salt of losartan according to claim 1 characterized in that it has the X-ray powder diffractogram as that shown in Figure 1.
3. Polymorphic form X of a potassium salt of losartan according to claim 1 characterized in that it exists in a crystalline form in the form of the solvate.
4. The process for the preparation of polymorphic form X of a potassium salt of losartan and the solvates thereof characterized by isolation from the mixture of methanol and hexane.
5. The process according to claim 4 characterized in that it comprises the following steps:
  - a) Preparation of a methanolic solution of a potassium salt of losartan,
  - b) concentrating of the resulting solution,
  - c) mixing of the resulting concentrated solution with hexane,
  - d) isolation of polymorphic form X of losartan potassium.
6. The pharmaceutical composition containing as the active substance polymorphic form X of potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole or the solvates thereof.
7. The use of polymorphic form X of a potassium salt of losartan for the preparation of a medicament.
8. The use of polymorphic form X of a potassium salt of losartan according to claim 7 for the preparation of a medicament for the treatment of hypertension.

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## Abstract

A new crystalline form of pharmaceutically suitable salt of 2-*n*-butyl-4-kloro-5-hidroksimetil-1-[[2'-(1H-tetrazol-5-il)[1,1'-bifenil]-4-il]metil]-1H-imidazole characterized with XRPD at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 in 29.2° has been prepared from other polymorph forms from a combination of solvents comprising methanol.

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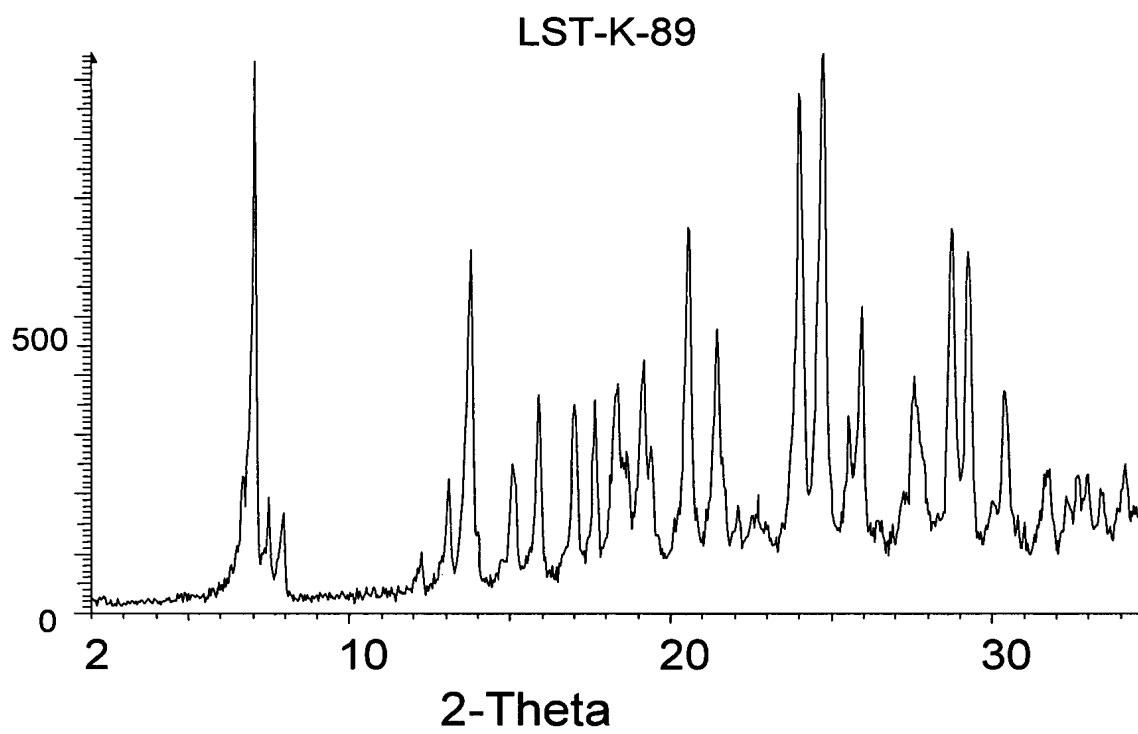


Figure 1

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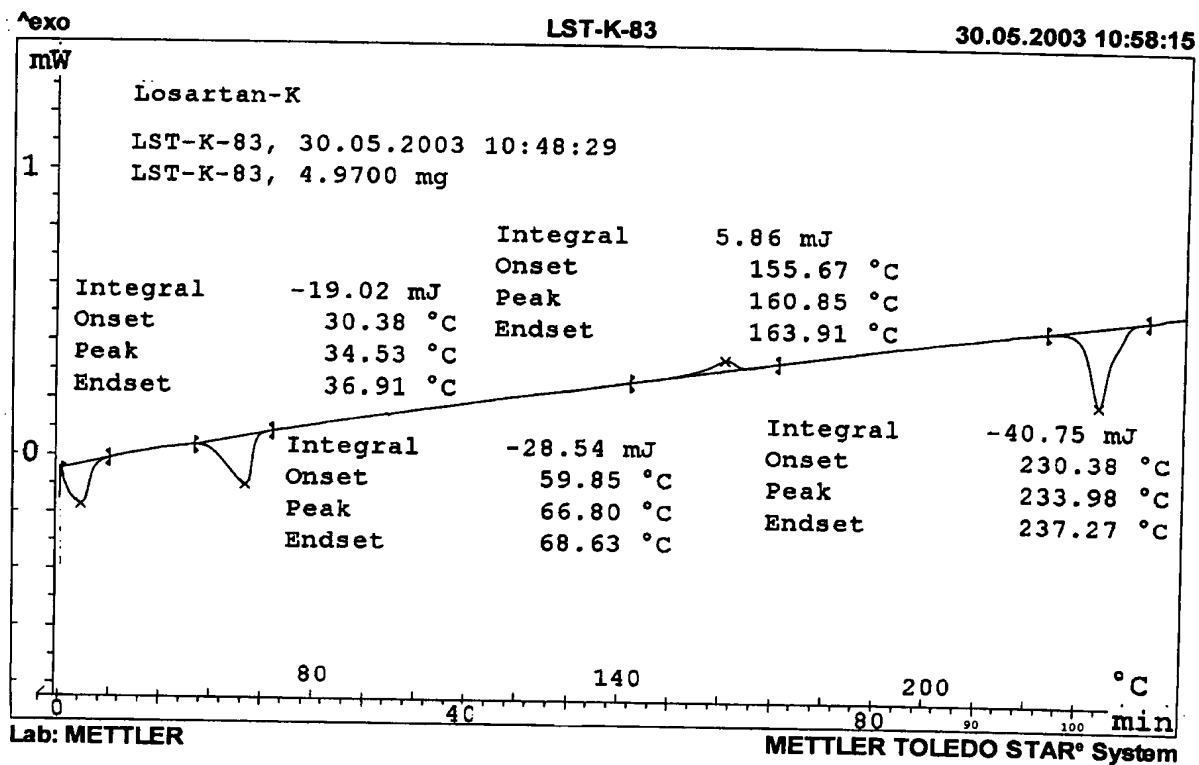


Figure 2

The undersigned Djurdjica Mandrino, permanent court interpreter for the English language, appointed by Decree No. 756-4/91, issued on 11<sup>th</sup> of February 1991 by the Ministry of Justice and Administration, Republic of Slovenia, hereby declares that this document entirely corresponds to the original Slovene text.

Ljubljana, 8 June 2005

